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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,223	02/23/2004	Thomas Maciag	536895013CT1	3032

23973 7590 10/22/2007

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
10/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,223	MACIAG ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-5, 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's After-Final Response, filed 1 October 2007, is acknowledged and entered. Applicant's substitute specification is acknowledged and entered. Applicant's statement that no new matter has been added is acknowledged. However, it is noted that the text spacing of the substitute specification differs from the originally submitted text spacing. Thus, references to page numbers in previously cited office actions may not correspond to the page numbers of the amended specification, filed 1 October. Any references to page numbers of the specification made hereafter will refer to the page numbers from the amended specification filed 1 October 2007.

It is also noted that Applicant's claims, filed 1 October 2007, did not contain the appropriate mark-ups of claim amendments. Applicant's attention is drawn to the Advisory Action of 9/11/2007, noting that the claim amendments filed 8/23/2007 were not entered. Thus, it is improper for Applicant to submit unmarked up claims as the Examiner would not readily know which changes have been made (see MPEP 714). However, in order to expedite prosecution, the Examiner is entering the claims filed 1 October 2007 with the mark-ups shown in the claim submission of 8/23/2007. It does not appear that any changes to the claims occurred between the 8/23/2007 claim set and the 10/1/2007 claim set. Applicant is strongly encouraged to follow the guidelines set forth in MPEP 714. Applicant's representative may also wish to contact the Inventor's Assistance Center for further clarification of patent prosecution procedure. Contact information for the IAC is available through the USPTO's website or at 571-272-1000.

In light of newly discovered references the examiner has reconsidered the finality of the rejections in the last Office action and, therefore, the **finality of that action is withdrawn**.

This action is NON-FINAL.

2. Claims 1-20 are pending. Claims 1-5 and 14-20 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 6-13 are under examination.

3. The indicated allowability of claims 7-8 and 11-13 is withdrawn in view of the newly discovered references set forth below. Rejections based on the newly cited references follow.

Response to Arguments

Objections/Rejections Withdrawn

4. The objection to the specification because of the informalities related to IL-1α and the misspelling of TTM on page 5, is withdrawn in light of Applicant's amendments to the specification.

5. The objection over claim 6 because of the informalities related to "IL[1]-α release" is withdrawn in light of Applicant's amendment.

New Claim Rejections

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Applebaum et al., (Free Radic Biol Med. 1990;8(2):133-43) (abstract only).

Claim 6 is drawn to methods of inhibiting neointima formation following vessel injury in a mammal comprising administering an amount of a copper chelator.

Applebaum et al., teach the effect of neocuproine (a highly effective chelator for both iron and copper, as well as with adventitious copper and with the combination of neocuproine and copper), on cardiac injury using retrogradely perfused isolated rat hearts in two experimental systems. In the first system, where hydrogen peroxide-induced damage was studied, neocuproine at the range of 40-175 μM provided protection at the level of 70-85%, as demonstrated by the reduced loss in the peak systolic pressure (P), in +dP/dt and in -dP/dt. In the second system, where ischemia/reperfusion-induced arrhythmias were studied, neocuproine (42 μM) provided a marked protection against cardiac injury as demonstrated by the lowering of the incidence in irreversible ventricular fibrillation, by decreasing the duration of ventricular fibrillation and by the concomitant increase of the duration of normal sinus rhythm, and by improving the post-ischemic recovery of P, +dP/dt and -dP/dt.

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. In re Hack, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978). In the instant case, because the Applebaum reference teaches the administration of a copper chelator (the same compound as the instant

claim 7) to the same population (mammals with vessel injury) the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability, particularly in light of the fact that Applebaum et al., teaches neocuproine at the range of 40-175 μM provided protection at the level of 70-85%, as demonstrated by the reduced loss in the peak systolic pressure (P), in +dP/dt and in -dP/dt.

8. Claims 6, 9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Brewer et al., WO 200013712 (published 16 March 2000).

The claims are drawn to methods of inhibiting neointima formation, macrophage infiltration following vessel injury, cell proliferation, extracellular matrix formation following arterial wall injury, and adventitial angiogenesis associated with arterial wall injury by administering a copper chelator.

WO 00/13712 teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis (pages 3 and 55-56), by administering the copper chelator tetrathiomolybdate (pp. 19- 25) (compare claims 6, 9, 11-13). WO 00/13712 teaches that disorders such as the "wet" type of macular degeneration occurs when abnormal new blood vessels or neovascular membranes grow from the choroid through the damaged pigment epithelium and under the macula (p. 54). These neovascular membranes are fragile and are prone to hemorrhage, which results in severe distortion of the macular tissue (p. 54). Other diseases associated with corneal neovascularization include epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratistis, Sjogren's syndrome, chemical burns, bacterial ulcers, herpes simplex infections, Kaposi sarcoma, rheumatoid arthritis, systemic lupus erythmatosus, trauma, diabetic retinopathy, macular degeneration, vein occlusion, artery occlusion, chronic inflammatory diseases, and atherosclerosis (pp. 55-57). Atherosclerotic plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity (p. 57, first paragraph). WO 00/13712 teaches that tetrathiomolybdate forms a stable tripartite complex with copper and protein (p. 18, line 28-29). WO 00/13712 teaches the treatment of diseases characterized by aberrant angiogenesis and neovascularization based on modulation of total-body copper status because copper is a required co-factor for the function of many key mediators of angiogenesis (p. 18, lines 4-9). WO 00/13712 teaches administration of tetrathiomolybdate in a non-anemia inducing amount of 20mg six times a day in patients with Wilson's disease (p. 22, lines 7-8). High dose ranges encompass 350-1400 mg/day (p. 22, line 18) and dose ranges of 25-50 mg day (p. 22, line 20) are taught as being well tolerated with no adverse side effects.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brewer et al., WO 200013712 (published 16 March 2000), Wang et al., (Biochem. Biophys. Res. Commun. 2000 271:138-143), and Wempe et al., (Arterioscler Thromb Vasc Biol. 1997 Nov;17(11):2471-8).

The Examiner finds the following facts:

a. The instant claims are drawn to methods of inhibiting neointima formation, macrophage infiltration following vessel injury, cell proliferation, extracellular matrix formation following arterial wall injury, and adventitial angiogenesis associated with arterial wall injury by administering a copper chelator.

b. WO 00/13712 teaches a method of treating neovascularization, aberrant vascularization, and aberrant angiogenesis (pages 3 and 55-56), by administering the copper chelator

tetrathiomolybdate (pp. 19- 25). WO 00/13712 teaches that disorders such as the "wet" type of macular degeneration occurs when abnormal new blood vessels or neovascular membranes grow from the choroid through the damaged pigment epithelium and under the macula (p. 54). These neovascular membranes are fragile and are prone to hemorrhage, which results in severe distortion of the macular tissue (p. 54). Other diseases associated with corneal neovascularization include epidemic keratoconjunctivitis, vitamin A deficiency, contact lens overwear, atopic keratistis, Sjogren's syndrome, chemical burns, bacterial ulcers, herpes simplex infections, Kaposi sarcoma, rheumatoid arthritis, systemic lupus erythmatosus, trauma, diabetic retinopathy, macular degeneration, vein occlusion, artery occlusion, chronic inflammatory diseases, and atherosclerosis (pp. 55-57). Atherosclerotic plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity (p. 57, first paragraph). WO 00/13712 teaches that tetrathiomolybdate forms a stable tripartite complex with copper and protein (p. 18, line 28-29). WO 00/13712 teaches the treatment of diseases characterized by aberrant angiogenesis and neovascularization based on modulation of total-body copper status because copper is a required co-factor for the function of many key mediators of angiogenesis (p. 18, lines 4-9). WO 00/13712 teaches administration of tetrathiomolybdate in a non-anemia inducing amount of 20mg six times a day in patients with Wilson's disease (p. 22, lines 7-8). High dose ranges encompass 350-1400 mg/day (p. 22, line 18) and dose ranges of 25-50 mg day (p. 22, line 20) are taught as being well tolerated with no adverse side effects.

c. WO 00/13712 does not teach a method of treating arterial wall injury following balloon angioplasty.

d. Wang et al., teach the differential but concomitant expression of IL-1 family mRNAs after balloon angioplasty suggests that IL-1 system components may play a distinct role in neointima formation (abstract). The neointima development is a natural response of the arterial wall to injury, and is based on time-dependent infiltration of the arterial wall with inflammatory cells as well as on up-regulation of growth factors and inflammatory cytokines.

e. Wempe et al., teach macrophage infiltration after vessel injury (abstract). Preferential adhesion of monocytic cells to migrating endothelial cells is demonstrated *in vivo* after balloon denudation injury of rat aortas (p. 5 of 16, second paragraph).

f. The level of skill of those in the art encompasses skills in the field of molecular biology relating to neovascularization and angiogenesis.

g. A person of ordinary skill in the art at the time the invention was made would have reasonably know that the copper chelator tetrathiomolybdate was used for treating conditions such as trauma, neovascularization, and angiogenesis. Further, a person of ordinary skill in the art would have been able to inhibit neointima formation, macrophage infiltration, cell proliferation associated with arterial wall injury, secretion of extracellular matrix following arterial wall injury, and adventitial angiogenesis by using well-known methodologies and protocols, such as the ones taught by WO 00/13712 in light of the teachings of Wang et al., and Gray et al.

h. Because the WO 00/13712 reference teaches administration of the same compound as the instant claims (tetrathiomolybdate) to the same population (mammals with vessel injury, inflammation, and arterial wall injury), the mechanism by which the recited inhibition occurs (i.e. in an non-traditional IL-1α release amount) has no bearing on patentability. The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. In re Hack, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978).

In view of the facts recited above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention. WO 00/13712 teaches administration of tetrathiomolybdate to a population comprising mammals with diseases characterized by aberrant angiogenesis, neovascularization, inflammation, and trauma, including choroidal neovascularization. Vessel and arterial wall injury is specifically taught in the model of "wet" macular degeneration (choroidal neovascularization), which is accompanied by hemorrhages in vessels of the eye. Angiogenic stimulatory activity of atherosclerotic plaques formed within the lumen of blood vessels is also taught. Macrophage infiltration after vessel injury is taught by Wempe et al., who demonstrate preferential adhesion of monocytic cells to the endothelial cells at the migration front *in vivo* after balloon denudation injury of rat aortas (p. 5 of 16, second paragraph). Wang et al., also teach neointima formation as a result of coronary angioplasty, which is indicative of arterial wall injury.

Applicants have previously stated that "an IL-1α release inhibiting amount" is set forth in the specification at Example 2 (page 48 of the specification as originally filed) as 10mg/kg to rats (see

Response, filed 12 January 2007, p. 14, second paragraph) with no adverse side effects. WO 00/13712 teaches administration of tetrathiomolybdate within this range (see above).

The person of ordinary skill in the art could have combined the elements as claimed by known methods to treat arterial wall injury following balloon angioplasty in light of the teachings of Wempe et al., and Wang et al., showing neointima formation and monocytic cell activation and infiltration following balloon angioplasty. One of skill in the art would have recognized that the results of the combination of administering the copper chelator tetrathiomolybdate to these related, but different patient populations would have would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made.

Conclusion

12. The prior art made of record and not presently relied upon is considered pertinent to applicant's disclosure.

Wang et al., US Patent Publication US 2003/0055113 (20 March 2003, benefit to 1 December 2000), teach methods of treating ocular inflammation using copper chelators.

Brewer et al., US Patent 6,703,050 (9 March 2004, benefit to 4 September 1998), teach methods using copper chelators for treatment of disorders involving angiogenesis.

NO CLAIMS ARE ALLOWED.

This action is NON-FINAL.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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